> principally. The one of skill would readily recognize that with the administration of one or more water-soluble HMG-CoA reductase inhibitors for metabolic diseases and disorders for which they are readily indicated, that in the process of treatment adiponectin would be affected. Arita and Weyer fully establish that the target population which suffers from an array of these metabolic disorders shares a link to the decrease in adiponectin or hypoadiponectinemia as genetically distinguished in Kondo et al.

Regarding Orsi, the Action contends that a preference for water-soluble HMG-CoA reductase inhibitors may be gleaned from this reference. *Id.*

Applicants respectfully disagree with these assertions. In particular, evidence previously submitted by applicants in response to the prior obviousness rejection counters the conclusions drawn in the present Action with respect to the new obviousness rejection (see Request for Continued Examination filed March 6, 2009 ("the RCE")). This evidence, in the form of exhibits and explanation, demonstrated that there was no reasonable expectation of success with respect to the claimed methods at the time the application was filed. While the present Action does not discuss this evidence, it was presumably persuasive because the prior obviousness rejection was overcome. Although the present Action relies upon a different combination of references to support the new obviousness rejection, the evidence remains just as persuasive here because the present Action attempts to show that the claimed methods would have been expected to work at the time the application was filed.

KSR confirmed that the Graham Factor Analyses should be used in determining whether a claimed invention is obvious under 35 U.S.C. § 103(a). *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007). Therefore, the following subsections set forth the (1) rejected claims; (2) scope and content of the cited art (Arita, Kondo, Ellsworth, Weyer, and Orsi) and the differences between the rejected claims and the cited art; and (3) an explanation as to why these differences are not rendered obvious by these references.

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A. The Rejected Claims

Independent Claim 41 is drawn to a method for increasing adiponectin production in a warm-blooded animal comprising administering to a warm-blooded animal in need of such treatment an effective amount of one or more HMG-CoA reductase inhibitor(s). Claims 43-47 depend from Claim 41. Independent Claim 48 is drawn to a method for treatment of hypoadiponectinemia in a warm-blooded animal comprising administering to a warm-blooded animal in need of such treatment an effective amount of one or more water-soluble HMG-CoA reductase inhibitor(s). Claims 55-57 and 59-62 depend from Claim 48.

B. Scope and Content of the Cited Art, and Differences Between the Rejected Claims and the Cited Art

(i) Arita

Arita discusses a cDNA expressed in adipose tissue and its gene product, adiponectin. Arita, p 79. The levels of adiponectin in the blood plasma of obese and non-obese individuals were measured and found to be less in obese individuals compared with non-obese individuals. *Id.* at pp 82-83. Arita notes that obesity frequently accompanies insulin resistance, hypertension, dyslipoproteinemia and vascular diseases. *Id.* at p 79.

Compared to the content of the rejected claims, Arita not only fails to mention any methods of increasing adiponectin production or treatment of hypoadiponectinemia in a warm-blooded animal, this reference also fails to discuss using HMG-CoA reductase inhibitors (water-soluble or otherwise) in such methods. The Action concedes the latter point. Action, p 5.

(ii) Kondo

Kondo presents data showing that blood plasma adiponectin concentrations of subjects carrying an I164T mutation in the adiponectin gene were significantly lower than control subjects not carrying the mutation. Kondo, p 2326. All subjects studied by Kondo carrying this mutation showed some feature of metabolic syndrome, including hypertension, hyperlipidemia,

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diabetes and atherosclerosis. *Id.* A majority of subjects with the mutation (5/9) had lipid abnormalities and were on hypolipidemic agents. *Id.* at 2326 and Table 2.

As conceded by the Action, this reference fails to discuss HMG-CoA reductase inhibitors (water-soluble or otherwise) to increase adiponectin production or treat hypoadiponectinemia in a warm-blooded animal. Action, p 5. Indeed, this reference fails to discuss HMG-CoA reductase inhibitors in any context.

(iii) Ellsworth

Ellsworth presents C-aryl glycosides as inhibitors of sodium dependent glucose transporters (SGLT2) found in the intestine and kidney. Ellsworth, Col. 1, lines 10-12. Such compounds may be used in the treatment of diabetes and diabetic complications, hyperinsulinemia, obesity, hypertriglyceridemia, Syndrome X, hyperlipidemia, atherosclerosis, and related diseases. *Id.* at Col. 1, lines 10-16, and Col. 7, lines 32-44. These compounds may be used in combination with lipid lowering agents such as HMG-CoA reductase inhibitors for these treatments as well. *Id.* at Col. 31, lines 27-30. A variety of HMG-CoA reductase inhibitors are listed, including pravastatin, lovastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin, and rosuvastatin. *See id.* at Col. 31-32 and Claim 23.

While Ellsworth discusses HMG-CoA reductase inhibitors, they are only mentioned as possible agents to use in combination with C-aryl glycosidic SGLT2 inhibitors. In contrast to the rejected claims, then, they are not mentioned as agents for monotherapy. Moreover, they are not mentioned as agents for increasing adiponectin production or for hypoadiponectinemia treatment. Indeed, adiponectin and hypoadiponectinemia are not mentioned by Ellsworth at all.

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(iv) Weyer

Weyer demonstrates that obesity and Type 2 diabetes are associated with low plasma adiponectin concentrations in different ethnic groups. Weyer, Abstract. The teachings of Weyer align with those of Arita, as noted by the Examiner. Action, p 6.

Weyer does not discuss modulation, much less increasing, adiponectin production using HMG-CoA reductase inhibitors. Treatment of hypoadiponectinemia using water-soluble HMG-CoA reductase inhibitors is also not mentioned. These are at least two differences between the rejected claims and the teachings of Weyer.

(v) Orsi

Orsi discusses a case of a patient experiencing memory loss while taking simvastatin and notes that members of the statin family may be used to treat dyslipidemias. Orsi, Abstract. Orsi's analysis includes a comparison of lipophilicities of various HMG-CoA reductase inhibitors. *Id.* at p 2. Simvastatin is characterized as being the most lipophilic of the statins, while lovastatin, atorvastatin, fluvastatin, cerivastatin, and pravastatin are, in order, less lipophilic. *Id.* While Orsi does not explicitly make a correlation between lipophilic statin use and memory loss (and even cites to studies showing no cognitive differences in patients ingesting either simvastatin or pravastatin), the memory loss experienced by the patient resolved after stopping simvastatin treatment, and it did not recur with pravastatin treatment. *Id.* at p 3.

While Orsi discusses HMG-CoA reductase inhibitors and their relative water solubilities, this reference does not discuss adiponectin or increasing production thereof, nor is hypoadiponectinemia or the treatment thereof discussed.

C. The Differences Between The Rejected Claims and the Cited Art Are Not Obvious Differences

The Action cites to Arita, Kondo, and Weyer for evidence that decreased adiponectin levels are associated with certain conditions (e.g., obesity, metabolic syndrome, and Type 2

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diabetes). As noted above, none of these references discuss HMG-CoA reductase inhibitors. Ellsworth is cited for its teachings of using HMG-CoA reductase inhibitors in combination therapy to treat these and similar types of conditions. Neither adiponectin nor hypoadiponectinemia is mentioned by Ellsworth, and it is only by virtue of using an HMG-CoA reductase inhibitor in combination with a C-aryl glycoside can the methods of Ellsworth treat the range of conditions discussed therein. Orsi is said to provide motivation for the selection of water-soluble HMG-CoA reductase inhibitors for treatment of hypoadiponectinemia, although this reference fails to discuss this condition.

Despite the lack of any evidence in these references that "the increase of adiponectin will occur" upon HMG-CoA reductase inhibitor administration, the Action makes this conclusion and the obviousness rejection is based on this conclusion. Action, p 9. See also Action, p 11: "[O]ne of skill would readily recognize that with the administration of one or more water-soluble HMG-CoA reductase inhibitors for metabolic diseases . . . adiponectin would be affected." As such, the Action appears to contend that administration of an HMG-CoA reductase inhibitor to a subject suffering from, e.g., hyperlipidemia, diabetes, or obesity, would have been expected to result in an increase of adiponectin production and, in the case of a water-soluble HMG-CoA reductase inhibitor, the treatment of hypoadiponectinemia. However, not only are the Action's arguments conclusory, but at the time the application was filed, there was no expectation that such results would occur. Indeed, applicants previously provided evidence (e.g., journal articles and explanations thereof) of this lack of expectation in the RCE. As such, the obviousness rejection is unsupported and should be withdrawn. See M.P.E.P. § 2142 ("The examiner bears the initial burden of factually supporting any *prima facie* case of obviousness.").

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(i) The Action's reasoning is conclusory

Citing *KSR*, the M.P.E.P. notes that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." M.P.E.P. § 2143.01 (citing *KSR*, 127 S. Ct. at 1741) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). However, in stating that administration of an HMG-CoA reductase inhibitor will increase adiponectin and that a water-soluble HMG-CoA reductase inhibitor will treat hypoadiponectinemia, the Action relies upon such improper conclusory statements.

For example, as indicated by Ellsworth and Orsi as well as the present specification, HMG-CoA reductase inhibitors may be used to treat hyperlipidemia. That the art teaches that hyperlipidemia may be associated with certain other physiological states, including low adiponectin levels as described by Arita, Kondo, and Weyer, does not permit a conclusion that an antihyperlipidemia agent such as an HMG-CoA reductase inhibitor will necessarily increase adiponectin production or, in the case of water-soluble HMG-CoA reductase inhibitors, treat hypoadiponectinemia. This is akin to concluding that because a patient having a headache may also be suffering from a viral infection (e.g., the flu or meningitis), it necessarily follows that administering aspirin will lower the viral count load in the patient. Yet the Action makes a similar illogical leap on pages 9 and 11 in stating that an HMG-CoA reductase inhibitor would necessarily raise adiponectin production, or treat hypoadiponectinemia in the case of a water-soluble HMG-CoA reductase inhibitor, in a hyperlipidemic patient simply because that patient suffered from a condition found to be associated with low adiponectin levels.

Moreover, lack of support for such a conclusion was established in the RCE, incorporated herein, where several exhibits were presented and discussed showing that "the Examiner's conclusion that the mechanism of action of statins would necessarily lead to increases in

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adiponectin levels is not supported by the knowledge of one skilled in the art as of the filing date of the present application." RCE, p 6. Although the Action does not explicitly refer to the mechanism of HMG-CoA reductase inhibitors in the present Action, applicants' previous arguments and evidence apply here to show the impropriety in the Action's present reasoning. For example, Sakamoto (RCE, Exhibit E, p 1018) states, "The precise mechanism(s) for the increase in adiponectin concentrations associated with pravastatin [an HMG-CoA reductase inhibitor] therapy is unknown." As Sakamoto is a June 2006 article, this reference supports the contention that the means by which an HMG-CoA reductase inhibitor may affect adiponectin production was unknown at the time the application was filed. See also Shetty, October 2004 (RCE, Exhibit C, pp 2455-6) (despite experiments designed to study atorvastatin and adiponectin levels, further study is required to understand adiponectin modulation). This uncertainty demonstrates that any assertion that an HMG-CoA reductase inhibitor would obviously and definitively "increase" or "affect" adiponectin production (Action, pp 9, 11) is unfounded and cannot support an obviousness rejection.

(ii) At the time the application was filed, there was no reasonable expectation that administration of a HMG-CoA reductase inhibitor would increase adiponectin production or that administration of a water-soluble HMG-CoA reductase inhibitor would treat hypoadiponectinemia

The Action's reasoning behind the obviousness rejection is also based on the assumption that, at the time the application was filed, it would have been reasonable to expect that administration of an HMG-CoA reductase inhibitor would successfully increase adiponectin production and that administration of a water-soluble HMG-CoA reductase inhibitor would successfully treat hypoadiponectinemia. However, applicants' RCE provided evidence to the contrary. Summarizing the information in the submitted exhibits, applicants noted: "Indeed, the weight of the evidence supports the novelty and non-obviousness of the claimed methods,

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because four out of five studies that measured adiponectin levels after treatment with various HMG-CoA reductase inhibitors found either no increase or decrease in adiponectin levels." RCE, p 6.

Moreover, even if it was obvious to try to administer HMG-CoA reductase inhibitors to increase adiponectin production, as suggested by the Action and which applicants do not concede, data offered by applicants demonstrates that the outcome of such efforts was unpredictable at the time the application was filed. In combination with applicants' showing that the claimed methods did not have a reasonable expectation of success at the time the application was filed, any assertion that the method of the rejected claims was "obvious to try" is improper. See *KSR*, 127 S. Ct. at 1740 (affirming that that section 103 bars patentability unless "the improvement is more than the predictable use of prior art elements according to their established functions").

III. Claim 41 Is Not Rendered Obvious By A Combination Of References That Include Orsi

It appears that the Action relies, in part, on Orsi to assert that Claim 41 is obvious. As noted above, Orsi is cited for the proposition that use of a water-soluble HMG-CoA reductase inhibitor would be obvious to increase adiponectin production or treat hypoadiponectinemia. However, Claim 41 does not recite a water-soluble HMG-CoA reductase inhibitor. As such, applicants disagree with any reliance upon Orsi for the obviousness rejection of Claim 41. Clarification of the citation of Orsi for this rejection is respectfully requested.

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CONCLUSION

Applicants believe that Claims 41, 43-48, 55-57, and 59-62 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1649.

Respectfully submitted,

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